The Examiner has required that a specific reference to prior non-provisional application and its current status be inserted in the first sentence of the application.

Claims 1, 6-7, 9-10, 12-13, 18, 20-21, 24 and 30 stand rejected under 35 USC §102(b) as being anticipated by Weintraub et al, U. S. Patent No. 4 013 785.

Claims 1-7, 9-10, 12-13, 17-24, 26 and 30 stand rejected under 35 USC §102(b) as being anticipated by Akkerboom et al, U. S. Patent No. 5 211 958.

Claims 1-3, 6-7, 9-10, 12-13, 16-24, 26 and 30 stand rejected under 35 USC §102(b) as being anticipated by Murphy et al, U. S. Patent No. 5 256 699.

Claims 4-5, 8, 11 and 14-15 stand rejected under 35 USC §103(a) as being unpatentable over Murphy, et al, U. S. Patent No. 5 256 699 in view of Remington.

Claims 33 and 34 are newly added. Support for Claim 33 can be found on Page 2, lines 23-25 of the specification and in Claim 1. Support for Claim 34 can be found on Page 4, lines 17-18 of the Specification and original Claim 5, and the Abstract. Therefore, Claims 33 and 34 do not introduce new matter into the application.

PRIORITY

The first sentence of the specification has been amended to specifically refer to Patent Application Serial No. 09/327 135, filed June 7, 1999 and to note that it has been issued as U. S. Patent No. 6 177 101.

THE REJECTION OF CLAIMS 1, 6-7, 9-10, 12-13, 18, 20-21 24 AND 30 UNDER 35 USC §102(B) AS BEING ANTICIPATED BY WEINTRAUB ET AL, U. S. PATENT NO. 4 013 785

Weintraub, et al, U. S. Patent No. 4 013 785 (The '785 patent) does not anticipate Claim 1 for the following reason.

Present Claim 1 is directed to a non-sustained release, non-chewable pharmaceutical tablet composition which comprises 60% of a rapidly precipitating drug and at least one of 2 to

25% of a binder and 6 to 40% of a superdisintegrant, wherein the drug is a fairly soluble or highly soluble salt form of a poorly soluble free base or free acid drug or anhydrous form of a poorly soluble free acid or free base. The soluble salts of poorly soluble amino and poorly acidic drugs when placed in water generate a supersaturated state with an initial solubility higher than that of the parent free acid or free base. Thus, it is believed that the drugs in the claimed tablet composition, in their more soluble salt form, results in more rapid absorption and higher bioavailability, prepared with HPMC or other listed excipients or compared to tablets of the parent drug salt. Support for the newly recited definition of the drug form can be found on page 3, lines 16-19 of the specification and hence it does not constitute new matter.

For a reference to anticipate a claim, the reference must disclose each limitation of the claim. Weintraub et al disclose an analgesic tablet containing n-acetyl-p-aminophenol (APAP) and fumed silica and a process for manufacturing the tablet. The tablet may also include binders, disintegrants, lubricants and diluents. While they disclose that other drugs may be incorporated into the tablet, they clearly state, column 2, lines 18-20, that the active material in the preferred embodiment will "consist essentially of APAP". Hence they do not disclose or suggest a tablet that contain any of these drugs except in combination with APAP.

The tablet defined in Claim 1 requires that the drug be a fairly soluble or highly soluble salt form of a poorly soluble free base or an anhydrous form of a poorly soluble free base or free acid drug. APAP does not fall within this limitation. Hence the '785 Patent does not anticipate Claim 1.

Since Weintraub et al does not anticipate generic Claim 1, it does not anticipate Claims 6-7, 9-10, 12-13, 18, 20-21, 24 and 30 all of which add limitations to and are

dependent from Claim 1. For Example Claim 33 requires that the tablet composition be prepared without heating, solvent or grinding. The Weintraub et al tablets are prepared by utilizing heating, solvents and grinding. Further, the binder in Claim 34 is limited to hydroxypropyl methylcellulose. Weintraub et al neither discloses or suggests the use of hydroxypropyl methylcellulose as a binder.

THE REJECTION OF CLAIMS 1-7, 9-10, 12-13, 17-24, 26 AND 30 UNDER 35 USC §102(b) AS BEING ANTICIPATED BY AKKERBOOM, ET AL, U. S. PATENT NO. 5 211 958

Claim 1 is not anticipated by U. S. Patent No. 5 211 958 (the '958 Patent) for the following reason: The '958 Patent discloses a multi-purpose pharmaceutical tablet comprising tetracyclines, microcrystalline cellulose or micro-fine cellulose, low substituted hydroxypropylcellulose and a thickening agent, preferably hydropropyl methylcellulose, and optional other conventional adjuvants. The form of the drug in the '958 Patent is defined as follows:

> "The invention is particularly suitable for the formulation of doxycycline, especially in the form of a hydrate, in particular the monohydrate, or any other form having a sufficiently low solubility to be virtually tasteless. Further suitable tetracyclines are, for example, tetracycline trihydrate, oxytetracycline dihydrat and the calcium salt of chlorotetracycline."

The formulations of the '958 Patent thus require the use of drugs in forms that have low solubility and are hydrated, whereas the formulations of the claimed invention require the use of drugs in forms that are fairly or highly soluble or are anhydrous.

The '958 Patent discloses one such drug in salt form, i.e., calcium chlorotetracycline. This salt is less soluble than chlorotetracycline, especially at the pH range of the intestine, pH 6.2-2.8. Therefore, calcium chlorotetracycline

does not meet the requirement of new Claim 1 for a fairly or highly soluble salt of a poorly soluble drug.

The invention defined in Claim 1 addresses a different problem from that addressed in the '958 Patent, i.e. precipitation. For a drug, as defined in Claim 1, that is soluble in salt form, if that salt form changes (i.e., to the free base or another salt of the drug) the resulting species is less soluble and thus becomes supersaturated. The supersaturation process leads to the tendency of poorly soluble drugs to precipitate from solution. In the claimed invention, excipients like HPMC apparently provide a precipitation delaying function. This inhibition of precipitation improves the bioavailability of the drugs.

As indicated above, calcium chlorotetracycline is insoluble. However, the hydrochloride salt of chlorotetracycline is highly water-soluble. It generates a supersaturated state and the free base precipitates out rapidly in water. This is well documented in the literature. Many soluble salts of poorly soluble acids or bases behave in this way. The present invention proposes that a tablet formation of chlorotetracycline HC with HPMC should result in improved dissolution and generation of a supersaturated state; this supersaturated state should result in more rapid oral absorption and it could provide higher oral bioavailability.

THE REJECTION OF CLAIMS 1-3, 6-7, 9-10, 12-13, 16-24, 26 AND 30 UNDER 35 USC §102(b) AS BEING ANTICIPATED BY MURPHY, ET AL

Claim 1 is not anticipated by Murphy, et al, U. S. Patent No. 5 256 699 (the '699 Patent) for the following reason: The '699 Patent discloses a dispersible solid drug formulation of diclofenac in the form of a tablet. It does not disclose or suggest that the diclofenac is in the form of either a fairly/highly soluble salt or an anhydrous form of a poorly

soluble free base or free acid. As a matter of fact the inventors specifically teach that the form of diclofenac preferred and used, the free acid, is poorly soluble. See column 1, lines 22-29 where it is stated:

> "If diclofenac sodium is incorporated in a dispersable tablet it dissolves when the tablet is dispersed in water or other suitable liquid producing a liquid with an undesirable bitter taste. diclofenac potassium also produces a liquid with a bitter taste.
>
> We have found that the difficulty is overcome if diclofenac is dispersed as the free acid rather than as a salt. <u>This has a low solubility and is virtually tasteless."</u>

Claim 1 also requires the presence of a binder in the amount of about 2% to about 20%. The amount of hydroxpropyl methylcellulose, in Murphy et al is less than 1% as is acknowledged by the Examiner.

Since generic Claim 1 is not anticipated by Murphy et al, neither are dependent Claims 2, 3, 6, 7, 9, 10, 12, 13, 16-24, 26, 30, 33 and 34 all of which add limitations to and are dependent from Claim 1.

The '699 patent also does not render Claim 1 obvious because it teaches away from using the soluble form of a drug.

THE REJECTION OF CLAIMS 4-5, 8, 11 AND 14-15 STAND REJECTED UNDER 35 USC §103(a) AS BEING UNPATENABLE OVER MURPHY, ET AL, U. S. PATENT NO. 5 256 699 IN VIEW OF REMINGTON

Claims 4-5, 8, 11 and 14-15 are patentably distinguishable over the '699 Patent in view of Remington for the following reason. The difference between the invention defined in these claims and the tablets disclosed in the '699 Patent have been set forth in the above discussion of the rejection of claims 1-3, 6, 7, 9, 10, 12, 13, 16-24, 26 and 30 under 35 USC §102(b). The

Remington reference does not cure the above noted defects of the '699 Patent.

In view of the amendments contained in this Response, as well as the above presented arguments, withdrawal of the objection and rejections and expeditious passage of this application to issue is respectfully solicited.

Respectfully submitted,

Sidney B. Williams, Jr.

SBWJ\pcq

FLYNN, THIEL, BOUTELL & TANIS, P.C.
2026 Rambling Road
Kalamazoo, MI 49008-1699
Phone: (616) 381-1156
Fax: (616) 381-5465

Dale H. Thiel	Reg. No. 24 323
David G. Boutell	Reg. No. 25 072
Ronald J. Tanis	Reg. No. 22 724
Terryence F. Chapman	Reg. No. 32 549
Mark L. Maki	Reg. No. 36 589
David S. Goldenberg	Reg. No. 31 257
Sidney B. Williams, Jr.	Reg. No. 24 949
Liane L. Churney	Reg. No. 40 694
Brian R. Tumm	Reg. No. 36 328
Tricia R. Cobb	Reg. No. 44 621

Encl: Marked-up Version of Amendments
Postal Card

136.0112

IN THE SPECIFICATION

Page 1 paragraph 1:

This application claims the benefit of US provisional application Serial no. 60/088,960 filed 11 June 1998, under 35 USC §119(e)(i). This application is a continuation of U. S. application Serial No. 09/327,135 filed June 7, 1999, now U. S. Patent No. 6 177 101.

IN THE CLAIMS

1. (Twice Amended) A non-sustained release, non-chewable tablet composition which comprises: a rapidly precipitating drug in an amount from about 5 to about 60%~~, microcrystalline cellulose,~~ and at least one member selected from the group consisting of a binder in an amount of from about 2 to about 25% and a superdisintegrant in an amount from about 6 to about 40% ~~where the rapidly precipitating drug, microcrystalline cellulose, binder and superdisintegrant are mixed and compressed into a tablet without heating, solvent or grinding,~~ wherein the rapidly precipitating drug is a fairly soluble or highly soluble salt form of a poorly soluble free base or anhydrous form of a poorly soluble free base or free acid, with the proviso that the rapidly precipitating drug is not delavirdine mesylate.

10. (Twice Amended) A non-sustained release, non-chewable pharmaceutical tablet composition according to Claim ~~1~~9 where the microcrystalline cellulose is selected from the group consisting of

microcrystalline cellulose coarse powder
microcrystalline cellulose medium powder and
microcrystalline cellulose 200.

12. (Twice Amended) A non-sustained release, non-chewable pharmaceutical tablet composition according to Claim ~~1~~9 where the microcrystalline cellulose is present in an amount of from about 10 to about 40%.